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THE INFECTIOUS DISEASES

RECENT ADDITIONS TO OUR KNOWLEDGE OF THEIR ETIOLOGY[1]

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Realizing how little time the general practitioner has to devote to reading the journals in which the results of experimental work are usually first reported, I have chosen for my subject a discussion of some recent additions to our knowledge of the etiology of the infectious diseases. Some of this work has been reported in publications not readily accessible and is of so great importance to all physicians, especially those in general practice and in public health work, that I am glad of this opportunity to review it.

These additions to our knowledge of the infectious diseases have been, up to the present time at least, of more practical value in the diagnosis and prevention of the particular diseases than in their cure. As general practitioners of medicine you are greatly interested in all advances that may assist you in diagnosis; and as the first to be aware of the presence in the community of infectious diseases you constitute the advance guard of your State health organization and are therefore concerned with methods of prevention.

It has not been many years since the aim of medical men, especially those in general practice, was to cure diseases while paying but slight attention to their prevention. But with the increase in our knowledge of the communicable diseases has come into practice a new branch of medical science, that of preventive medicine, and this has been recognized in our medical schools by the establishment of chairs of preventive medicine.

Our knowledge of the etiology of infectious diseases has advanced, not uniformly, but by leaps and bounds as new methods have been developed and new incentives have arisen. With the evolution of a bacteriological technic, led by Pasteur and Koch, there was, for a few years, a rapid expansion in our knowledge of bacterial infections. The discovery that Texas fever of cattle was transmitted by the tick started extensive studies in the relation of insects to the transmission of diseases. The demonstration that certain diseases are due to ultramicroscopic organisms—so-called "filterable viruses"—rapidly led to a study of many diseases of obscure etiology and cleared away much of the confusion in regard to them.

Again, great epidemics have furnished the incentive for the most exhaustive study of some of our essentially epidemic diseases, such as cholera, plague, influenza, meningitis, and poliomyelitis.

While very recent years have seen great advance in our knowledge of many of the phenomena of disease—in our understanding of its physiology—there was a period not long since in which little was done to advance our knowledge of some important infectious diseases endemic almost throughout the civilized world, and research workers realized that new methods or agencies must be employed. As a result of the use of certain methods or agencies of research, the value of which had not been previously generally recognized or employed, there has been in the last few years a great increase in our knowledge of this class of diseases.

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Along with these advances in our knowledge of those diseases considered for years as infectious has come the discovery that certain diseases formerly thought not to be communicable do after all belong to the infectious class. I refer especially to poliomyelitis, which for years was considered to be a degenerative disease of the nervous system, and which recent researches have proved to belong among the infectious diseases.

The use of the monkey as an experimental animal instead of the lower animals usually employed has contributed more than any other single factor to the important recent additions to our knowledge of the acute infections. Recent work has shown that the monkey is susceptible to a number of diseases that affect man and which are not readily or not at all transmissible to the small laboratory animals, such as rabbits, rats, and guinea pigs. We have thus been able to reproduce these diseases, and to study them under laboratory conditions.

Another important advance was in the adoption of methods of experiment by which the infective material was introduced into the body so that it was brought into immediate contact with the organs or tissues primarily and most seriously affected in the natural disease, as in experimental meningitis and poliomyelitis, where the infective material is put directly into the cranial or spinal cavities.

Other factors of value have been the recognition of the fact that the same disease may present a very different clinical picture in one species as compared with another, even to a difference in postmortem findings, and yet be due to the same etiological agent. Filtration through earthenware filters, by means of which contaminating organisms are removed; greater experience in interpreting results; the training and development of men for research; the foundation and endowment of institutions for research, have all contributed to what we know of the communicable diseases.

After this somewhat general discussion of the factors contributing to advances in our knowledge of the communicable diseases, I shall now discuss briefly some recent work on certain of these diseases.

Poliomyelitis.

Students of the epidemiology of poliomyelitis had begun to realize that this disease belonged to the infectious class before Landsteiner and Popper in 1909 had shown for the first time that the disease could be transmitted to monkeys by inoculation with an emulsion of the spinal cord from a child who died on the fourth day of an attack of infantile paralysis. Since then, as the result of an immense amount of work done both in this country and abroad, many important facts have been discovered in regard to the nature of the virus and the channels by which it may enter and leave the body.

It has been shown that the disease may be transmitted by inoculation to monkeys and occasionally to rabbits. The disease belongs among the filterable viruses; that is, its virus is capable of passing through earthenware filters and is so minute that it probably can not be seen except by the use of special methods, even with the highest powers of the microscope. It has been shown that the virus is present in various organs of human beings dead from poliomyelitis and that the tonsils of monkeys five months after the acute stage of the disease still contain the infective agent. The same is probably true of human beings, and such persons might well become sources of infection.

Kling, Wernstedt, and Petterson have shown that poliomyelitis may be produced in monkeys by the inoculation of filtered washings from the mouth and nose, from the trachea, and from the small intestine, collected at autopsy from cases of infantile paralysis dying in the early stages of the disease.

Of special importance was their report that they had succeeded in demonstrating for the first time the virus of the disease in the buccal and intestinal secretions of persons who gave no history of recent illness, but who had come into intimate contact with other persons in their families sick with poliomyelitis. The opinion was expressed that such virus carriers were most likely very common during epidemics of poliomyelitis, probably exceeding the number of persons with clinically recognizable infections.

These findings would have almost justified the conclusion that the infection of poliomyelitis is disseminated by the transfer of the virus directly from person to person; but doubt was cast upon the validity of such a conclusion as a result of the report by Rosenau on the possible agency of the stable fly as a transmitter of the disease. Rosenau showed that in a certain proportion of cases the disease could be transmitted from sick to healthy monkeys by the bite of the stable fly. This work was partially corroborated by Anderson and Frost; but subsequent work by these latter investigators and by others have tended to show that probably the stable fly is not the usual factor by which the disease is transmitted.

The next important advance in our knowledge of the etiology of poliomyelitis was announced by Flexner and Noguchi, from the Rockefeller Institute. These workers showed that by employing special methods of culture they had been able to cultivate from the central nervous tissues of human beings and monkeys the subjects of acute poliomyelitis, a peculiar minute organism, and that with such cultures they had been able to produce the symptoms and lesions of poliomyelitis.

The microorganism described by these workers consists of globoid bodies of extremely small size arranged in pairs, chains, and masses, according to the conditions of growth and multiplication. They were unwilling to express themselves as to the place among living things to which the bodies belonged, but stated that the cultural conditions necessary are those applying more particularly to the bacteria. They were able to produce typical poliomyelitis in monkeys by inoculation with the twentieth generation of cultures from the originally infected animal.

We are still without definite knowledge as to the methods of spread and prevention of the disease.

Measles.

Measles may be said to be practically a world-wide disease, one that is always endemic and often epidemic, especially in our larger cities; but in spite of the toll in deaths that it yearly exacts, the large number of persons that it incapacitates for varying periods by illness, and the serious complications and sequelæ, measles is too often regarded by physicians and the laity as a necessary incident of childhood. The disease was the cause of 44,080 deaths in the registration area for deaths of the United States during the period 1900 to 1910. The number of deaths as compared with those of certain other diseases in the registration area for deaths during 1910 is shown in the following table:

Disease.	Deaths.	Deaths per 100,000 population.
Diphtheria and croup	11,512	21.4
Measles	6,598	12.3
Scarlet fever	6,255	11.6
Whooping cough	6,148	11.4
Cerebrospinal meningitis	2,272	4.2
Infantile paralysis	1,459	2.7

While it has been quite the general belief among clinicians for many years that the infective agent of measles is contained in the blood, in the nasal and buccal secretions, and perhaps in the "scales," the experimental data in support of this belief previous to 1911 were very incomplete.

But the work of Anderson and Goldberger on measles converted what had previously been opinions based on clinical observations into proven facts based on laboratory experiments. These authors showed that the monkey was susceptible to infection with measles by inoculation with blood from human cases of the disease. They showed that the apparent insusceptibility of the monkey to infection with measles was largely due to a limitation of the period of infectivity of the blood to the very early stages of the disease before or shortly after the appearance of the eruption. Thirty-six hours after the first appearance of the eruption the infectivity of the blood for the monkey becomes greatly lessened and rapidly decreases. Studies on the nature of the virus as it exists in the circulating blood showed that the infective agent is capable in a certain proportion of cases of passing through a Berkefeld filter and therefore is included among the filterable viruses.

Experiments made to test the infectivity of the nasal and buccal secretions from human cases of measles showed that such secretions, collected within the first 48 hours after the appearance of the eruption, were infective for monkeys by subcutaneous inoculation; this would correspond to about the fourth and sixth days of the disease.

Experiments made to determine the duration of the infectivity of these secretions strongly suggested a reduction if not a total loss of their infectivity with the approach of convalescence. Attempts were made, without success, to demonstrate the presence of the infective agent of measles in the "scales" collected from human cases of the disease from four to seven days after the appearance of the eruption.

Since the work of Anderson and Goldberger was reported, three papers by different workers have been published corroborating their results as to the presence of the virus in the blood of human cases and the susceptibility of the monkey to measles. Hektoen and Eggers, while chiefly concerned in their work on experimental measles in the monkey with a study of the leucocytes, state that the general results of their experiments agree very well with those reported by Anderson and Goldberger.

Nicolle and Conseil have reported the infection of the bonnet monkey with measles by the inoculation of blood drawn 24 hours before the appearance of the eruption. And more recently Lucas and Prizer have reported the observation of Koplik spots in monkeys experimentally infected with measles.

The results of these studies on measles give us our first definite information, based on carefully controlled laboratory experiments, as to the nature of the virus, its means of exit from the body and the probable avenue of infection. The experimental observations on the duration of infectivity of the secretions are in accord with previous clinical observations, that cases of the disease are as a rule not infective after convalescence is well established. The great importance of having definitely determined this point, and the further one as to the noninfectivity of the "scales," from a public health aspect can readily be appreciated.

Scarlet Fever.

Scarlet fever and measles rank close together in our morbidity and mortality reports, and I shall now briefly refer to some recent investigations of scarlet fever which offer a hope that the discovery of the cause of this disease may not be far distant.

Early in 1911 Cantacuzène and also Bernhardt reported independently the production of scarlet fever in the lower monkeys, using as a source of infection lymph glands, blood, pericardial fluid, and scrapings from the tongue of scarlet fever patients. Both authors claimed to have obtained in monkeys a febrile reaction, attended with an eruption, appearing after a variable incubation period and followed by desquamation of the skin.

Cantacuzène did not mention any lesions of the throat, but was very positive in affirming that his monkeys were infected with scarlatina. Bernhardt claimed to have succeeded in transmitting the infection from monkey to monkey, but denied the specific relationship of the streptococcus and believed that the infective agent of scarlatina should be classed among the filterable viruses.

Just about the time that these observations were reported Landsteiner, Levaditi, and Prasek, in a preliminary note, reported some attempts on the transmission of scarlet fever to chimpanzees, and in a subsequent paper presented their work in detail. They endeavored to infect chimpanzees with scarlet fever by various methods of inoculation, using blood, emulsion of lymph glands, and deposits from the tonsils of cases of scarlet fever. In two out of four experiments the chimpanzees developed a reaction very striking in its resemblance to scarlet fever in the human being. In the other two chimpanzees the inoculations were followed only by angina without any cutaneous manifestations.

These experimental researches show that the inoculation of material from scarlet fever patients into monkeys is followed sometimes by a morbid syndrome which resembles more or less that of scarlet fever in human beings. Amongst the monkeys the anthropoids appear to present a susceptibility more constant than the lower monkeys.

The disease produced experimentally seems to be caused by the specific virus of scarlet fever, and the streptococcus does not appear to bear any etiological relationship to the disease. If we admit the scarlatinal nature of the infection, which to me appears very probable, it is then permissible to conclude that the virus of the disease exists in the deposits on the tonsils and tongue, in the blood, the lymphatic nodes, and perhaps in the pericardial fluid. As to the nature of the etiological agent of scarlet fever we are still almost totally without knowledge. It is hoped that further experimental work will result in more definite knowledge as to the etiology and mode of transmission of the disease than that which we have already accumulated.

Typhoid Fever.

It has now been over 30 years since Eberth first described the *Bacillus typhosus,* and 30 years since Gaffky isolated the same organism in pure culture. But in spite of the fact that the study of the typhoid bacillus is a matter of almost universal practice in all laboratories and that many are engaged in clinical and epidemiological studies of the disease, experimental proof that the typhoid bacillus is the specific cause of this infection has been scant. In view of this apparent lack of advance there are many, even in this day, who question whether the bacillus described by Eberth is really the specific etiological agent of typhoid fever. Recently there has appeared work, the results of which show that this skepticism is not justified and that the typhoid bacillus is the specific etiological agent of typhoid fever.

Grunbaum in 1906 made attempts to infect chimpanzees with typhoid fever by feeding them pure cultures and also by feeding a portion of the stool from a case of typhoid fever; but his results, while very suggestive, were not conclusive.

In March, 1911, Metchnikoff and Besredka presented a paper on experimental typhoid fever in the chimpanzee, reporting work which is of so much interest and importance that I think a few words on it may not be without interest to you. Metchnikoff and Besredka, having in mind the history of hog cholera, instead of using pure cultures of the typhoid bacillus endeavored to infect a chimpanzee with the feces of a case of typhoid fever containing an abundance of typhoid bacilli. The chimpanzee, eight days after ingestion of the fecal material mixed with food, developed typhoid fever. The appearance of diarrhea, the presence of typhoid bacilli in the blood, and the development of specific agglutinins in the blood serum, left no doubt as to the result and clearly showed the susceptibility of the chimpanzee to infection with typhoid fever by feeding.

They were unable to either infect or vaccinate apes by the feeding and injection under the skin of the fluid obtained by the filtration of typhoid stools. From this the authors conclude that the typhoid bacillus, and not a filterable virus, is the etiological agent in typhoid fever. They found that the lower monkeys are only exceptionally susceptible to typhoid fever, and that rodents, such as the rabbit and guinea pig, are not at all susceptible to infection by feeding.

In the same paper, and also in a later one, they report attempts at protective inoculation by various means. They found that neither killed cultures nor their autolysates protected chimpanzees against infection with typhoid fever, but that vaccination with living cultures produced an immunity apparently as definite as from an attack of the disease. Vaccination with nonsensitized cultures produced an intense local and general reaction, while sensitized cultures caused only a feeble local and almost no general reaction; both appeared to confer equal immunity to infection. The work reported by Metchnikoff and Besredka fulfills for the first time the postulates of Koch as to the etiological relation of the *Bacillus typhosus* to typhoid fever, discredits the theory of a filterable virus in the disease, shows the possibility of absolute protection by vaccination with living cultures, and emphasizes the importance of not relying upon vaccination with killed cultures alone to the exclusion of all other precautionary measures.

Whooping Cough.

In 1900 Bordet and Gengou reported the observation, in sputum from whooping-cough cases, of a small bacillus, which was not obtained by them in pure culture until six years later, and gave certain reasons in support of their opinion that the bacillus discovered by them was the cause of whooping cough. Among these reasons was the fact that the bacillus described by them was found only in cases of whooping cough and was always present in the earliest stages of the disease; another reason being that it was found that the patient's blood serum contained an antibody, which was specific for this organism and which could be demonstrated by the complement fixation test.

More recently Mallory and his coworkers have confirmed and extended the findings of Bordet and Gengou in regard to the etiological relationship to whooping cough of the bacillus described by the former workers. Mallory and his associates have found that the primary single lesion in whooping cough consists of the presence of masses of minute bacilli between the cilia of the epithelial cells lining the trachea and bronchi. They consider that their action is chiefly mechanical by interfering with the normal movements of the cilia by causing them to stick together, and in this way furnishing a continual irritation, which results in the symptoms peculiar to the disease. They have been able, with sputum from cases of whooping cough and with pure cultures of an organism corresponding in every way with that described by Bordet and Gengou, to produce the same characteristic lesion in young animals and to obtain the organism again in pure culture from those animals.

They have therefore been able to fill the gaps which have heretofore existed, according to Koch's law, for the complete demonstration that the Bordet Gengou bacillus is the cause of whooping cough. They consider that the action of the bacilli in the respiratory tract would seem to be largely mechanical by their presence in such large numbers that they must interfere with the normal ciliary action and thus with the removal of secretion and of inhaled particles. At the same time, the organism probably produces a mild toxin, which is evidenced by the production of the well-recognized lymphocytosis, and by the production of an antibody which is found present in the blood.

The organism is most abundant and most easily demonstrated in the early stages of the disease. This corresponds with the clinical observation that the disease is most readily communicable at that time.

The disease is transmitted by the secretions from the mouth and throat, and is most infectious in the early stages.

Typhus Fever.

The last appearance of typhus fever in the United States in epidemic form was in New York in 1891–92. Since then, except for an occasional case at some of our large seaports, it has been believed that the disease had been eradicated from this country.

It has been a source of wonder to health authorities that, in spite of the occasional arrival in this country of immigrants sick with typhus and of many persons from endemic foci of the disease, typhus fever apparently did not gain a foothold in the United States. That this had already taken place has recently been shown through the demonstration by Anderson and Goldberger in the Hygienic Laboratory, United States Public Health Service, that a disease observed and studied in New York City by Dr. Nathan E. Brill is identical with typhus fever.

As far back as 1896 Dr. Brill began to notice from time to time among his typhoid cases types that were distinguishable from typhoid and paratyphoid fevers because of the short duration of the fever, the presence of a distinctive eruption, and the absence of specific agglutination reactions. He continued his observations on this type of fever and published two papers based on the study of 255 cases observed up to December, 1910.

About the time that Brill's second paper appeared, Anderson and Goldberger were engaged in the study of the typhus fever of Mexico and having the picture of that disease clearly in mind, were struck by the very marked clinical resemblance between it and the disease described by Brill. Influenced by this resemblance, they endeavored to see cases of Brill's disease in order to determine, if possible, the relationship between that infection and typhus fever.

Their efforts to do this were not successful until September, 1911, when they saw a well-marked case of Brill's disease in the wards of Mount Sinai Hospital, New York. Blood drawn from the arm vein of this patient was used for the inoculation of monkeys, one of which, nine days after inoculation, developed a fever, which reached its maximum six days later. The fever lasted for 11 days, when it terminated by rapid lysis. Blood was drawn from this animal at the height of its fever and successfully used for the inoculation of other monkeys. Monkeys that have recovered from one attack are immune to subsequent infection. Since then the infection has been carried through 22 monkey generations by inoculation of blood, and is now being continued by passage through guinea pigs.

Having established the susceptibility of the rhesus monkey to inoculation with defibrinated blood from cases of the disease described by Brill, it became important to determine the relationship of that disease to typhus fever, and for this purpose they proceeded to Mexico City, taking monkeys that had recovered from infection with the virus originally obtained from case No. 1 of Brill's disease, as well as fresh animals for controls.

Without going into the details of their tests, it is sufficient to state that it was found that an attack of Brill's disease confers immunity to subsequent infection with Mexican typhus and, conversely, that an attack of typhus confers immunity to subsequent infection with Brill's disease. To put it in a simpler way: Brill's disease, so called, and typhus fever are identical.

During the progress of the work necessary for the demonstration of the identity of the so-called Brill's disease and Mexican typhus, attention was given to various problems relative to the mode of transmission. It was found that the New York disease, as also the typhus of Mexico, may be transmitted from monkey to monkey by the bite of body lice that had been allowed to feed on monkeys sick with the disease. These results were in harmony with and confirm those previously reported by them and by others.

They were unable to transmit the disease by the bite of bedbugs or by the inoculation of the buccal and pharyngeal secretions from a human case of typhus. They were also convinced that the only way by which typhus is transmitted is by the bite of the body louse and possibly by that of the head louse.

Now that it is shown that typhus fever is identical with Brill's disease and that Brill's disease has been endemic in the city of New York for a great many years, there is good reason to believe that what is true of New York is true also of other large American and Canadian cities. In fact, since this first work appeared cases have been reported from several cities.

When one recalls how frequently the mild forms of even the familiar infectious diseases are overlooked, it need occasion no surprise that the benign form of a disease, usually thought of in our country as an exotic disease, or at least, perhaps, as a medical curiosity, should fail of recognition. That this is not applicable to typhus alone is strikingly shown by the history of pellagra and of hookworm disease in the United States.

I wish to point out that the recognition of these mild forms of typhus gives us a rational explanation of what Osler has well characterized as a "remarkable feature" of typhus, namely, the occurrence of a few cases at long intervals of time from any other outbreaks and at great distances from any known foci of the disease. In other words, these mild forms constitute the missing epidemiological link between so-called sporadic cases or outbreaks. In the propagation of typhus this mild form plays somewhat the same rôle that the "missed" or the "carrier" cases do in such diseases as diphtheria and typhoid.

The demonstration of the endemic presence of typhus fever in the United States requires the American sanitarian to recognize the existence of a problem of which he has heretofore been unaware, and to be on his guard against a disease that presumably may at any time assume epidemic prevalence and virulence.

Future advances in our knowledge of the acute infections would seem to depend to a large extent upon the discovery of new methods of staining the etiological agent and of new methods of culture.

It is a singular and regretable fact that in spite of the large and important additions to our knowledge of the cause and means of transmission of many of the communicable diseases the application of this knowledge in the control and eradication of the diseases has not kept pace with its acquisition. With a few notable exceptions, such as the control of yellow fever through mosquito eradication and of bubonic plague by rat campaigns, health authorities have been slow to apply the great mass of information now available to them by reason of the researches of the last few years.

It would seem that what is most needed at the present time is not so much more research, but a more general application of the results already at hand. Research should of course be encouraged and developed; the laity, physicians, and health officers should be impressed with the importance of using the information already available, and very important it is that our lawmakers should also be made to see that it requires money to carry out the measures for the control of diseases along the lines which have been pointed out so convincingly by laboratory studies.